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(54) **New pharmaceutical preparation with controlled release of metoprolol, a method for the manufacture thereof and the use of the new preparation.**

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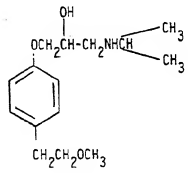
Description

The present invention is related to a new pharmaceutical preparation with controlled release of metoprolol, to a method for the manufacture of such a preparation and to a method for treatment of cardiovascular disorders using the new pharmaceutical preparation.

Metoprolol, which has the structural formula



is known from e.g. DE-2 106 209. The drug, which is a β-adrenoceptor antagonist has preferably been used as a salt, e.g. the tartrate.

Metoprolol blocks the adrenergic stimulation of the heart and thus reduces the oxygen demand of the cardiac tissue. Apparently, this explains its beneficial effects in angina pectoris and cardioprotective action in myocardial infarction. In addition metoprolol normalizes blood pressure in a large proportion of patients with arterial hypertension which probably is due to an additional action on the control of peripheral resistance to blood-flow.

For patients suffering from cardiovascular disorders it is advantageous to have a constant concentration of the administered drug in the blood. Thus, a controlled release of the drug over a long period of time is desirable. According to the most common treatment, the patients are ordered one fast dissolving tablet twice a day. This gives a varying concentration with high peak and trough values of the drug during the day.

For dosage once a day metoprolol has been incorporated in controlled release tablets of the insoluble matrix type, e.g. Durules®. However the drug release from the matrix tablets is not satisfying as about 50 per cent of the dose is released within a few hours after administration. It has thus been a demand to find a way to obtain a drug preparation having a more constant controlled release of the active component for approximately 20-24 hours, whereby smoother blood concentration and effect profiles will be obtained over the entire dosage interval.

A drug delivery system named Oros® may be used to obtain a controlled release of e.g. metoprolol for once daily dosage. The system is described in U.S. Patent 4 036 227 and in a supplement to British Journal of Clinical Pharmacology (1985), 19, 695-765 by Theeuwes F et al. Oros® is a single-unit system consisting of an osmotically active core composed mainly of the drug substance surrounded by a semipermeable membrane through which a single small opening is drilled. The release of the drug from the system remains constant as long as a steady osmotic pressure is maintained across the membrane. 50-60% of the total content of the drug is released at a constant rate.

In SE-A-8400085 it has been proposed to prepare an enteric coated product, containing e.g. metoprolol, and with slow release of the active compound close to the colon. Such a preparation does not give the constant and slow pH-independent release of metoprolol, which the preparation according to this invention gives.

Depot preparations comprising a large number of smaller units are also known e.g. from EP 13263. This patent describes pharmaceutically indifferent cores covered by the active compound. The cores are made of soluble material e.g. lactose.

There are advantages of a depot preparation comprising a large number of small units, each of which releases the drug at a controlled rate over a depot preparation consisting of one single unit, e.g. a matrix tablet or a tablet surrounded by a coating, which controls the release. It is possible to obtain a reproducible emptying of units from the stomach when the particles used are smaller than 1-2 mm. Cf. Bogentoft C et al. : Influence of food on the absorption of acetylsalicylic acid from enteric-coated dosage forms. Europ J Clin Pharmacol 1978, 14, 351-355. Dispersion over a great area in the gastrointestinal canal gives a more reproducible total time of the passage which is of advantage for the absorption. Cf. Edgar B, Bogentoft C and Lagerström P O : Comparison of two enteric-coated acetylsalicylic acid preparations by monitoring steady-state levels of salicylic

acid and its metabolites in plasma and urine. Biopharmaceutics & Drug Disposition 1984, 5, 251-260. In addition a multiple unit preparation is preferable to one single drug unit as the dose is spread out in the intestine. The risk of local irritation and accumulation of several doses due to constriction in the alimentary canal is also considerably lower.

A further advantage with a multiple unit preparation is that it may be divided into smaller portions all having the same absorption properties. This makes it possible to obtain greater flexibility in selecting the size of the dose.

Outline of the Invention

The present invention is related to a preparation containing metoprolol as active ingredient and having a controlled rate of drug release during at least 15 hours. By making a preparation containing a large number of small compact particles all comprising a salt of metoprolol as the main soluble component and coated with a polymeric membrane containing derivatives of cellulose without protolysable groups it has been possible to prepare a suitable dosage form having a controlled rate of release of metoprolol, virtually independent of pH, during 16-24 hours.

The small particles, beads, containing metoprolol have a size of 0.25-2 mm, preferably 0.35-1.0 mm.

The beads may contain metoprolol alone or may consist of insoluble cores coated with metoprolol. The beads have a very high content of metoprolol, preferably 95-100 w/w% of the soluble part of the beads. The insoluble cores have a size of 0.1-1.0 mm, preferably 0.15-0.3 mm. Examples of insoluble cores according to the invention are silicon dioxide and small particles of glass.

The beads according to the invention are compact, which means that their porosity is less than 15 per cent.

As can be seen from figure 1 the new preparation is characterized in that at least 75% of the metoprolol is released within 20 hours and at least 50% of the dose of metoprolol is released at the rate 3-7 w/w %/hour.

Metoprolol used in the preparation may be in the form of the racemate, or one of the enantiomers, preferably the S-isomer.

Suitable soluble salts of metoprolol have a solubility less than 600 mg/ml in water at 25°C, preferably 30-600 mg/ml in water at 25°C. Examples of suitable salts are salts formed of organic carboxylic acids, preferably of low molecular weight. Especially preferred are the succinate, fumarate or benzoate of racemic metoprolol and the benzoate or sorbate of the S-enantiomer of metoprolol.

Very soluble salts, e.g. tartrate, hydrochloride are less suitable according to the present invention.

Examples of suitable polymeric materials are ethyl cellulose or a mixture of ethyl cellulose with hydroxypropylmethyl cellulose, hydroxypropyl cellulose, Eudragit® RL or Eudragit® RS.

Ethyl cellulose is available in variants having different grades of viscosity. According to the invention it is suitable to use ethyl cellulose having a viscosity between 10-50 mPas but also other types of ethyl cellulose may be used.

Eudragit® is the trade name for a number of filmcoating substances on an acrylic resin basis produced by Röhm Pharma. Eudragit RL and RS are copolymers synthetized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the remaining neutral (meth)acrylic acid esters is 1 :20 for Eudragit RL and 1 :40 for Eudragit RS, resulting in different permeability characteristics.

Plasticizers and/or pigments may be added to the polymeric layer in order to improve the technical properties of the layer or change the permeability of the coating. Examples of suitable plasticizers are citrate esters, acetylated monoglycerides and glycerinetriacetate, especially preferred is acetyltributylcitrate.

The polymeric membrane is made of one or more polymers and gives a membrane with virtually pH-independent permeability characteristics within the pH range 1.0-8.0.

Each coated bead of metoprolol according to this invention forms an individual controlled release unit, releasing the drug at a predetermined rate. Therefore, the coated beads according to this invention make it possible to formulate and administer the preparation in different dosage forms. They can be filled into e.g. hard gelatin capsules or sachets or compressed to tablets and still give the desired plasma concentration profile and duration of the effect.

When the small coated particles of metoprolol are tabletted they are mixed with additives e.g. microcrystalline cellulose such as Avicel®, which improves the tabletting properties and facilitates the disintegration of the tablet, whereby the individual beads are liberated.

The invention makes it possible to formulate pharmaceutical dosage forms which can be given once daily and still produce almost constant concentrations of the drug in the blood during the entire dosage interval until the next dose is administered.

Preparation

A process for the manufacture of the controlled release preparation represents a further aspect of the invention. After the initial forming of the beads containing metoprolol, the beads obtained are coated with the polymeric layer described in the examples. The polymeric mixture is dissolved in an organic solvent such as ethanol, isopropyl alcohol and/or methylene chloride. The spraying can be carried out in a coating pan, but is preferably carried out in a fluidized bed. Ethyl cellulose can also be applied from an aqueous dispersion (latex).

The preparation according to the invention is particularly advantageous in the treatment of cardiovascular disorders, and a method for the treatment of such conditions represents a further aspect of the invention.

The invention is described in detail in the following examples :

EXAMPLES

Example 1

Metoprolol fumarate	1440 g
Methylene chloride	9618 g
Ethanol 95%	3888 g
SiO_2 (0.15-0.25 mm)	375 g

Polymeric layer

Ethyl cellulose 10 cps	265.6 g
Hydroxypropylmethyl cellulose	58.4 g
Acetyltributylcitrate	36.0 g
Methylene chloride	6141 g
Isopropylic alcohol	1544 g

In a fluidized bed granulator metoprolol fumarate was sprayed onto the cores of silicon dioxide from a solution of ethanol 95%. 400 g of the beads (granules) so formed (fraction 0.4-0.63 mm) were covered with the polymeric layer containing ethyl cellulose 10 mPas, hydroxypropylmethyl cellulose and acetyltributylcitrate by spraying a solution of the mentioned substances in methylene chloride and isopropyl alcohol. The coated beads were then filled into hard gelatine capsules.

Example 2

Metoprolol succinate	1440 g
Methylene chloride	9618 g
Ethanol 95%	3888 g
SiO_2 (0.15-0.25 mm)	375 g

Polymeric layer

Ethylcellulose 50 cps	168.1 g
Hydroxypropylmethyl cellulose	36.9 g
Acetyltributylcitrate	22.8 g
Methylene chloride	4167 g
Isopropylic alcohol	815 g

Tablet additives

Microcrystalline cellulose	470.3 g
Maize starch	117.6 g
Potato starch	10.6 g
Water purified	342.2 g
Magnesium stearate	1.2 g

Metoprolol succinate was sprayed onto the cores of silicon dioxide according to the process described in Example 1. 400 g of the granules so formed were coated with a polymeric film containing ethyl cellulose 50 cps, hydroxypropylmethyl cellulose and acetyltributylcitrate. An additional tablet mass was made by wet granulation of the dry mixture of microcrystalline cellulose and maize starch with the potato starchwater solution in a planetary mixer. Equal amounts (600 g) of the active and additional granules were finally mixed with Mg-stearate 0.1% and compressed to tablets.

Example 3

Metoprolol succinate 100% in the form of compact spherical granules and having an average particle size of 0.42 mm

400 g of the metoprolol succinate granules above with particles less than 0.63 mm were coated with

Ethylcellulose 10 cps	177.1 g
Hydroxypropylmethyl cellulose	38.9 g
Acetyltributylcitrate	24.0 g
Methylene chloride	4094 g
Isopropylic alcohol	1029 g

The beads obtained were formed into pharmaceutical preparations as described above.

Example 4

Metoprolol succinate	1440 g
Methylene chloride	9618 g
Ethanol 95%	3888 g
SiO_2 (0.15-0.25 mm)	375 g

Polymeric layer

Ethylcellulose N-10	166.2 g
Hydroxypropylmethyl cellulose	39.0 g
Acetyltributylcitrate	22.8 g
Methylene chloride	3889 g
Isopropylic alcohol	978 g

Tablet additives

Microcrystalline cellulose	429.3 g
Maize starch	67.1 g
Lactose powder	40.3 g
Polyvidone	55.5 g
Water purified	314.7 g
Magnesium stearate	1.2 g

Tablet coating (12.500 tablets)

Hydroxypropylmethyl cellulose	159.6 g
Polyethylene glycol 6000	39.9 g
Colour Titanium Dioxide	39.9 g
Water purified	1356 g
Paraffin special	1.6 g

Metoprolol succinate was sprayed onto the cores of silicon dioxide according to the process described in Examples 1 and 2 above. 400 g of the so obtained beads (fraction 0.4-0.63 mm) were coated with the polymeric mixture also described above. The coated beads of metoprolol succinate obtained were mixed with the additives in equal portions and after addition of Mg-stearate 0.1%, the dry mixture was compressed to tablets. Finally, the tablets were coated in a coating pan with the tablet coating described above.

Example 5

S-enantiomeric metoprolol sorbate in the form of compact spherical granules in the fraction 0.4-0.63 mm

40 g of the metoprolol sorbate granules above with particles less than 0.63 mm together with 360 g of non-pareil granules with particles between 0.75-1.0 mm were coated with

Ethylcellulose 10 cps	51.7 g
Hydroxypropylmethyl cellulose	11.3 g
Acetyltributylcitrate	7.0 g
Methylene chloride	1194 g
Isopropylic alcohol	300 g

The beads obtained were formed into pharmaceutical preparations as described above.

Biopharmaceutical studies

The plasma concentrations of metoprolol after a single dose of a controlled release preparation containing metoprolol succinate 190 mg according to example 4 of the description and the plasma concentrations after a single dose of Durules® containing 200 mg of metoprolol tartrate are shown in the attached Figure 2. 190 mg of the succinate salt is equivalent to 200 mg of metoprolol tartrate. The comparison has been carried out in 10 subjects. Each point represents the mean data from the 10 subjects. As can be seen the preparation according to the invention gives an almost constant concentration of metoprolol during more than 20 hours, whereas the insoluble matrix preparation gives unwanted high plasma concentration during the first hours after administration.

Reduction of exercise heart rate

12 subjects were given an ordinary tablet containing 100 mg of metoprolol tartrate once a day and the reduction of the exercise heart rate on day 5 of the treatment was measured and compared with the reduction of the exercise heart rate on day 5 in subjects given a controlled release preparation according to Example 4 of the invention containing 95 mg metoprolol succinate (equivalent to 100 mg metoprolol tartrate). The reduction of the heart rate is illustrated in Fig. 3. As can be seen the preparation according to the invention gives an even pharmacodynamic effect for 24 hours.

The best mode of carrying out the invention is at present considered to be Example 4.

Table 1 illustrates the in vitro release of metoprolol from the compositions according to Examples 1-4. As can be seen from the table at least 50% of the dose of metoprolol is released at a rate varying between 3-7 w/w %/hour.

Table 1. Cumulative in vitro dissolution of metoprolol in a phosphate buffer pH 6.8.
Method: USP apparatus No. II, rotating paddle at 100 rpm.

Example No.	Preparation	Per cent released over time (h)											
		1	2	3	4	6	8	10	12	14	16	18	20
1	capsule	1	2	5	11	25	39	52	62	69	74	78	81
2	tablet	7	11	16	19	29	40	50	59	68	76	82	86
3	capsule	3	7	12	17	27	37	44	52	60	67	74	80
4	tablet	7	13	18	23	33	43	52	61	69	76	82	86
5	capsule	4	9	15	21	34	47	58	67	74	80	84	88

Claims

Claims for the following Contracting States : BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Controlled release preparation of metoprolol which releases the active drug continuously over a period of at least 15 hours virtuallly independent of pH of the gastrointestinal tract characterized in that the preparation contains a plurality of beads, said beads comprising as the main soluble component at least 95 w/w % of a salt of metoprolol, which has a solubility of less than 600 mg/ml in water at 25°C and that each of said beads is coated with a polymeric membrane containing derivatives of cellulose without protolysable groups and whereby the main part of the drug is released at a rate of 3-7 w/w %/hour.

2. Preparation according to claim 1 **characterized** in that the size of beads is in the range of 0.25-2 mm.

3. Preparation according to claim **characterized** in that the size of the beads is in the range of 0.35-1.0 mm.

4. Preparation according to claim 1 **characterized** in that the beads have a porosity of less than 15%.

5. Preparation according to claim 1 **characterized** in that the salt of metoprolol has a solubility of 30-600 mg/ml.

6. Preparation according to claim 5 **characterized** in that the salt is formed of an organic carboxylic acid.

7. Preparation according to claim 6 **characterized** in that the salt of metoprolol is the succinate or fumarate of racemic metoprolol.

8. Preparation according to claim 6 **characterized** in that the salt of metoprolol is the benzoate or sorbate of the S-enantiomer of metopropol.

9. Preparation according to claim 1 **characterized** in that the uncoated beads comprise a salt of metoprolol applied on an insoluble core.

10. Preparation according to claim 9 **characterized** in that the insoluble cores have a size of 0.1-1.0 mm, preferably 0.15-0.3 mm.

11. Preparation according to claim 9 **characterized** in that the insoluble cores have a size of 0.15-0.3 mm and are covered by a salt of metoprolol to give beads having a size of 0.35-1.0 mm which are coated with the polymeric membrane.

12. Preparation according to claim 1 **characterized** in that the uncoated beads having a size of 0.35-1.0 mm comprise a salt of metoprolol as such and are coated with the polymeric membrane.

13. Preparation according to claim 1 **characterized** in that the polymeric membrane consists of ethyl cellulose.

14. Preparation according to claim 1 **characterized** in that the polymeric membrane consists of ethyl cellulose together with hydroxypropylmethyl cellulose.

15. A pharmaceutical preparation containing the controlled release preparation according to claim 1 **characterized** in that the coated beads are filled into hard gelatine capsules.

16. A pharmaceutical preparation containing the controlled release preparation according to claim 1 **characterized** in that the coated beads together with pharmaceutical additives are compressed to tablets which disintegrate into the primary formed coated beads when the tablets are brought into contact with gastro-intestinal fluids.

17. Method of producing a preparation according to claim 1 **characterized** in that beads comprising a salt of metoprolol as the main soluble component are spray coated with a membrane-forming solution containing derivatives of cellulose without protolysable groups.

18. Use of a preparation according to claim 1 in the manufacture of a pharmaceutical preparation for treatment of cardiovascular disorders.

Claims for the following Contracting States : AT, ES, GR

1. Process for the preparation of a controlled release preparation of metopropol which releases the active drug continuously over a period of at least 15 hours virtually independent of pH of the gastrointestinal tract **characterized** in that a plurality of beads comprising as the main soluble component at least 95 w/w % of a salt of metopropol which has a solubility of less than 600 mg/ml in water at 25°C are each spray-coated with a membrane-forming solution giving a polymeric membrane containing derivatives of cellulose without protolysable groups whereby a preparation is obtained which releases the main part of the drug at a rate of 3-7 w/w %/hour.

2. Process according to claim 1 **characterized** in that the size of the beads is in the range of 0.25-2 mm.

3. Process according to claim 2 **characterized** in that the size of the beads is in the range of 0.35-1.0 mm.

4. Process according to claim 1 **characterized** in that the beads have a porosity of less than 15%.

5. Process according to claim 1 **characterized** in that the salt of metopropol has a solubility of 30-600 mg/ml.

6. Process according of claim 5 **characterized** in that the salt is formed of an organic carboxylic acid.

7. Process according to claim 6 **characterized** in that the salt of metoprolol is the succinate or fumarate of racemic metoprolol.

8. Process according to claim 6 **characterized** in that the salt of metopropol is the benzoate or sorbate of the S-enantiomer of metoprolol.

9. Process according to claim 1 **characterized** in that the uncoated beads comprise a salt of metoprolol applied on an insoluble core.

10. Process according to claim 9 **characterized** in that the insoluble cores have a size of 0.1-1.0 mm, preferably 0.15-0.3 mm.

11. Process according to claim 9 **characterized** in that the insoluble cores have a size of 0.15-0.3 mm and are covered by a salt of metoprolol to give beads having a size of 0.35-1.0 mm which are coated with the polymeric membrane.

12. Process according to claim 1 **characterized** in that the uncoated beads having a size of 0.35-1.0 mm comprise a salt of metoprolol as such and are coated with the polymeric membrane.

13. Process according to claim 1 **characterized** in that the polymeric membrane consists of ethyl cellulose.

14. Process according to claim 1 **characterized** in that the polymeric membrane consists of ethyl cellulose together with hydroxypropylmethyl cellulose.

15. A process for the manufacture of a pharmaceutical preparation containing the controlled release preparation according to claim 1 **characterized** in that the coated beads are filled into hard gelatine capsules.

16. A process for the manufacture of a pharmaceutical preparation containing the controlled release preparation according to claim 1 **characterized** in that the coated beads together with pharmaceutical additives are compressed to tablets which disintegrate into the primary formed coated beads when the tablets are brought into contact with gastro-intestinal fluids.

17. Use of a preparation produced according to claim 1 in the manufacture of a preparation for treatment of cardiovascular disorders.

Patentansprüche

Patentansprüche Für folgenden Vertragsstaaten : BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Metoprololpräparation mit gesteuerter Freigabe, welche den aktiven Arzneistoff über einen Zeitraum von mindestens 15 Stunden praktisch unabhängig vom pH-Wert des Magen-Darm-Traktes kontinuierlich freigibt, dadurch gekennzeichnet, daß die Präparation eine Mehrzahl von Kügelchen enthält, welche Kügelchen als lösliche Haupt-Komponente zumindest 95 Gew./Gew.-% eines Metoprololsalzes enthalten, das eine Löslichkeit von weniger als 600 mg/ml in Wasser bei 25°C hat, und daß jedes der Kügelchen mit einer Polymermembran überzogen ist, die Cellulosederivate ohne protolysierbare Gruppen enthält, wobei der Hauptteil des Arzneistoffes mit einer Geschwindigkeit von 3-7 Gew./Gew.-%/Stunde freigegeben wird.

2. Präparation nach Anspruch 1, dadurch gekennzeichnet, daß die Größe der Kügelchen im Bereich von 0,25 bis 2 mm liegt.

3. Präparation nach Anspruch 2, dadurch gekennzeichnet, daß die Größe der Kügelchen im Bereich von 0,35 bis 1,0 mm liegt.

4. Präparation nach Anspruch 1, dadurch gekennzeichnet, daß die Kügelchen eine Porosität von weniger als 15% aufweisen.

5. Präparation nach Anspruch 1, dadurch gekennzeichnet, daß das Metoprololsalz eine Löslichkeit von 30-600 mg/ml hat.

6. Präparation nach Anspruch 5, dadurch gekennzeichnet, daß das Salz aus einer organischen Carbonsäure gebildet ist.

7. Präparation nach Anspruch 6, dadurch gekennzeichnet, daß das Metoprololsalz das Succinat oder Fumarat von racemischem Metoprolol ist.

8. Präparation nach Anspruch 6, dadurch gekennzeichnet, daß das Metoprololsalz das Benzoat oder Sorbat des S-Enantiomeren von Metoprolol ist.

9. Präparation nach Anspruch 1, dadurch gekennzeichnet, daß die nicht überzogenen Kügelchen ein auf einen unlöslichen Kern aufgebrachtes Metoprololsalz enthalten.

10. Präparation nach Anspruch 9, dadurch gekennzeichnet, daß die unlöslichen Kerne eine Größe von 0,1 bis 1,0 mm, vorzugsweise 0,15 bis 0,3 mm, aufweisen.

11. Präparation nach Anspruch 9, dadurch gekennzeichnet, daß die unlöslichen Kerne eine Größe von 0,15 bis 0,3 mm aufweisen und mit einem Metoprololsalz bedeckt sind, was Kügelchen mit einer Größe von 0,35 bis 1,0 mm ergibt, die mit der Polymermembran überzogen sind.

12. Präparation nach Anspruch 1, dadurch gekennzeichnet, daß die nicht überzogenen Kügelchen, die eine Größe von 0,35 bis 1,0 mm aufweisen, ein Metoprololsalz als solches enthalten und mit der Polymermembran überzogen sind.

13. Präparation nach Anspruch 1, dadurch gekennzeichnet, daß die Polymermembran aus Äthylcellulose besteht.

14. Präparation nach Anspruch 1, dadurch gekennzeichnet, daß die Polymermembran aus Äthylcellulose zusammen mit Hydroxypropylmethylcellulose besteht.

15. Pharmazeutisches Präparat enthaltend die Präparation mit gesteuerter Freigabe nach Anspruch 1, dadurch gekennzeichnet, daß die überzogenen Kügelchen in harte Gelatinekapseln gefüllt werden.

16. Pharmazeutisches Präparat enthaltend die Präparation mit gesteuerter Freigabe nach Anspruch 1, dadurch gekennzeichnet, daß die überzogenen Kügelchen zusammen mit pharmazeutischen Additiven zu Tabletten gepreßt werden, die in die primär gebildeten überzogenen Kügelchen zerfallen, wenn die Tabletten mit Magen-Darm-Flüssigkeiten in Kontakt gebracht werden.

17. Verfahren zur Herstellung einer Präparation nach Anspruch 1, dadurch gekennzeichnet, daß ein Metoprololsalz als lösliche Haupt-Komponente enthaltende Kügelchen mit einer membranbildenden Lösung, die Cellulosederivate ohne protolysierbare Gruppen enthält, durch Sprühen überzogen werden.

18. Verwendung einer Präparation nach Anspruch 1 bei der Herstellung eines pharmazeutischen Präparates zur Behandlung kardiovaskulärer Störungen.

Patentansprüche Für folgenden Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung einer Metoprololpräparation mit gesteuerter Freigabe, welche den aktiven Arzneistoff über einen Zeitraum von mindestens 15 Stunden praktisch unabhängig vom pH-Wert des Magen-Darm-Traktes kontinuierlich freigibt, dadurch gekennzeichnet, daß eine Mehrzahl von Kügelchen, die als lösliche Haupt-Komponente zumindest 95 Gew./Gew.-% eines Metoprololsalzes enthalten, das eine Löslichkeit von weniger als 600 mg/ml in Wasser bei 25°C hat, jeweils mit einer membranbildenden Lösung durch Sprühen überzogen werden, um eine Cellulosederivate ohne protolysierbare Gruppen enthaltende Polymermembran zu ergeben, wodurch eine Präparation erhalten wird, die den Hauptteil des Arzneistoffes mit einer Geschwindigkeit von 3-7 Gew./Gew.-%/Stunde freigibt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Größe der Kügelchen im Bereich von 0,25 bis 2 mm liegt.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die Größe der Kügelchen im Bereich von 0,35 bis 1,0 mm liegt.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Kügelchen eine Porosität von weniger als 15% aufweisen.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Metoprololsalz eine Löslichkeit von 30-600 mg/ml hat.

6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das Salz aus einer organischen Carbonsäure gebildet ist.

7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß das Metoprololsalz das Succinat oder Fumarat von racemischem Metoprolol ist.

8. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß das Metoprololsalz das Benzoat oder Sorbat des S-Enantiomeren von Metoprolol ist.

9. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die nicht überzogenen Kügelchen ein auf einen unlöslichen Kern aufgebrachtes Metoprololsalz enthalten.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß die unlöslichen Kerne eine Größe von 0,1 bis 1,0 mm, vorzugsweise 0,15 bis 0,3 mm, aufweisen.

11. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß die unlöslichen Kerne eine Größe von 0,15 bis 0,3 mm aufweisen und mit einem Metoprololsalz bedeckt sind, was Kügelchen mit einer Größe von 0,35 bis 1,0 mm ergibt, die mit der Polymermembran überzogen sind.

12. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die nicht überzogenen Kügelchen, die eine Größe von 0,35 bis 1,0 mm aufweisen, ein Metoprololsalz als solches enthalten und mit der Polymermembran überzogen sind.

13. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Polymermembran aus Äthylcellulose besteht.

14. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Polymermembran aus Äthylcellulose zusammen mit Hydroxypropylmethylcellulose besteht.

15. Verfahren zur Herstellung eines pharmazeutischen Präparates enthaltend die Präparation mit gesteuerter Freigabe nach Anspruch 1, dadurch gekennzeichnet, daß die überzogenen Kügelchen in harte Gelatinekapseln gefüllt werden.

16. Verfahren zur Herstellung eines pharmazeutischen Präparates enthaltend die Präparation mit gesteuerter Freigabe nach Anspruch 1, dadurch gekennzeichnet, daß die überzogenen Kügelchen zusammen mit pharmazeutischen Additiven zu Tabletten gepreßt werden, die in die primär gebildeten überzogener Kügelchen zerfallen, wenn die Tabletten mit Magen-Darm-Flüssigkeiten in Kontakt gebracht werden.

17. Verwendung einer nach Anspruch 1 hergestellten Präparation bei der Herstellung eines Präparates zur Behandlung kardiovaskulärer Störungen.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, IT, LI, LU, NL, SE

1. Préparation à libération réglée de métoprolol , qui libère la substance active en continu sur une période d'au moins 15 heures de façon virtuellement indépendante du pH du tube gastro-intestinal , caractérisée en ce que la préparation contient plusieurs perles , lesdites perles comprenant , comme principal constituant soluble , au moins 95 % en poids/poids d'un sel de metoprolol , qui a une solubilité de moins de 600 mg/ml dans de l'eau à 25 °C, et en ce que chacune desdites perles est enrobée dune membrane polymère contenant des dérivés de la cellulose sans groupes protolysables , et en ce que la majeure partie de la substance active est ainsi libérée à une vitesse de 3 à 7 % en poids/poids/heure.

2. Préparation selon la revendication 1 , caractérisée en ce que la taille des perles se situe dans la gamme allant de 0,25 à 2 mm.

3. Préparation selon la revendication 2 , caractérisée en ce que la taille des perles se situe dans la gamme allant de 0,35 à 1,0 mm.

4. Préparation selon la revendication 1 , caractérisée en ce que les perles ont une porosité inférieure à 15 %.

5. Préparation selon la revendication 1 , caractérisée en ce que le sel de metoprolol a une solubilité de 30 à 600 mg/ml.

6. Préparation selon la revendication 5 , caractérisée en ce que le sel est formé d'un acide carboxylique organique.

7. Préparation selon la revendication 6 , caractérisée en ce que le sel de metoprolol est le succinate ou fumarate de métoprolol racémique.

8. Préparation selon la revendication 6 , caractérisée en ce que le sel de metoprolol est le benzoate ou le sorbate de l'énantiomère S de métoprolol.

9. Préparation selon la revendication 1, caractérisée en ce que les perles non enrobées comprenant un sel de métoprolol appliqué sur un noyau insoluble.

10. Préparation selon la revendication 9 , caractérisée en ce que les noyaux insolubles ont une taille de 0,1 à 1,0 mm , de préférence 0,15 à 0,3 mm.

11. Préparation selon la revendication 9 , caractérisée en ce que les noyaux insolubles ont une taille de 0,15 a 0,3 mm,et en ce qu'ils sont recouverts d'un sel de métoprolol pour donner des perles ayant une taille de 0,35 à 1,0 mm et qui sont enrobées de la membrane polymère.

12. Préparation selon la revendication 1 , caractérisée en ce que les perles non enrobées mesurant de 0,35 à 1,0 mm comprennent un sel de metoprolol tel quel et sont enrobées de la matière polymère.

13. Préparation selon la revendication 1 , caractérisée en ce que la membrane polymère consiste en de l'éthyl cellulose.

14. Préparation selon la revendication 1 , caractérisée en ce que la membrane polymère consiste en de l'éthyl cellulose avec de l'hydroxypropylméthyl cellulose.

15. Préparation pharmaceutique contenant la préparation à libération réglée selon la revendication 1 , caractérisée en ce que les perles enrobées garnissent des capsules en gélatine dure .

16. Préparation pharmaceutique contenant la préparation à libération réglée selon la revendication 1 , caractérisée en ce que les perles enrobées sont comprimées avec des additifs pharmaceutiques en donnant des comprimés qui se désagrègent,en donnant les perles enrobées formées tout d'abord , lorsque les compri-

més sont mis en contact avec des fluides gastro-intestinaux.

17. Procédé pour produire une préparation selon la revendication 1 , caractérisé en ce qu'on enrobe des perles, comprenant un sel de métoprolol comme principal constituant soluble , par projection par pulvérisation d'une solution formatrice de membrane, contenant des dérivés de la cellulose sans groupes protolysables.

18. Utilisation d'une préparation selon la revendication 1 , dans la fabrication d'une préparation pharmaceutique pour le traitement de troubles cardio-vasculaires.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé pour la confection d'une préparation à libération réglée de metoprolol, qui libère la substance active en continu sur une période d'au moins 15 heures de façon virtuellement indépendante du pH du tube gastro-intestinal ,procédé caractérisé en ce qu'on soumet plusieurs perles , comprenant comme principal constituant soluble , au moins 95 % en poids/poids d'un sel de metopropol , qui a une solubilité de moins de 600 mg/ml dans de l'eau à 25 °C , à enrobage par projection par pulvérisation d'une solution formatrice de membrane donnant une membrane polymère contenant des dérivés de la cellulose sans groupes protolysables , de sorte qu'on obtient une préparation qui libère la majeure partie de la substance active à raison de 3 à 7 % en poids/poids par heure.

2. Procédé selon la revendication 1 , caractérisé en ce que la taille des perles se situe dans la gamme allant de 0,25 à 2 mm.

3. Procédé selon la revendication 2 , caractérisé en ce que la taille des perles se situe dans la gamme allant de 0,35 à.1,0 mm .

4. Procédé selon la revendication 1 , caractérisé en ce que les perles ont une porosité inférieure à 15 % .

5. Procédé selon la revendication 1 , caractérisé en ce que le sel de metoprolol a une solubilité de 30 à 600 mg/ml .

6. Procédé selon la revendication 5 , caractérisé en ce que le sel est formé d'un acide carboxylique organique .

7. Procédé selon la revendication 6 , caractérisé en ce que le sel de metoprolol est le succinate ou le fumarate de metoprolol racémique.

8. Procédé selon la revendication 6 , caractérisé en ce que le sel de metoprolol est le benzoate ou le sorbate de l'énantiomère S de métoprolol.

9. Procédé selon la revendliation 1 , caractérisé en ce que les perles non enrobées comprennent un sel de métoprolol appliqué sur un noyau insoluble.

10. Procédé selon la revendication 9 , caractérisé en ce que les noyaux insolubles mesurent de 0,1 à 1,0 mm , de préférence 0,15 à 0,3 mm.

11. Procédé selon la revendication 9 , caractérisé en ce que les noyaux insolubles mesurent de 0,15 à 0,3 mm et sont recouverts d'un sel de metoprolol pour donner des perles mesurant de 0,35 à 1,0 mm,qui sont enrobées de la membrane polymère.

12. Procédé selon la revendication 1 , caractérisé en ce que les perles non erobées,mesurant de 0,35 à 1,0 mm , comprennent un sel de metoprolol tel quel et sont enrobées de la membrane polymère.

13. Procédé selon la revendication 1 , caractérisé en ce que la membrane polymère consiste en de l'éthyl cellulose .

14. Procédé selon la revendication 1 , caractérisé en ce ce que la membrane polymère consiste en de l'éthyl cellulose avec de l'hydroxypropylméthyl cellulose.

15. Procédé pour la fabrication d'une préparation pharmaceutique contenant la préparation à libération réglée selon la revendication 1 , caractérisé en ce que les perles enrobées sont versées dans des capsules en gélatine dure.

16. Procédé pour la fabrication d'une préparation pharmaceutique contenant la préparation à libération réglée selon la revendication 1 , caractérisé en ce que les perles enrobées sont comprimées avec des additifs pharmaceutiques pour donner des comprimés qui se désagrègent, en donnant les perles enrobées formées au début , lorsque les comprimés sont mis en contact avec des fluides gastro-intestinaux.

17. Utilisation d'une préparation produite selon la revendication 1 dans la fabrication d'une préparation pour le traitement de troubles cardio-vasculaires.

FIGURE 1 . IN VITRO RELEASE OF METOPROLOL RATE PLOT (%/h) VERSUS TIME

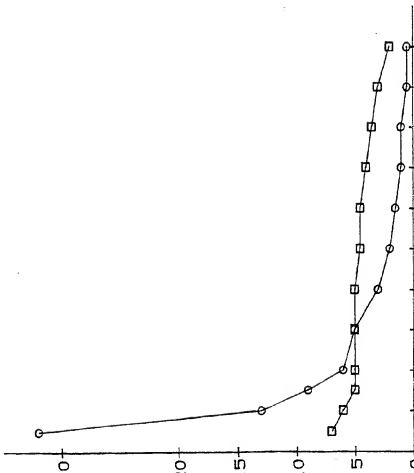
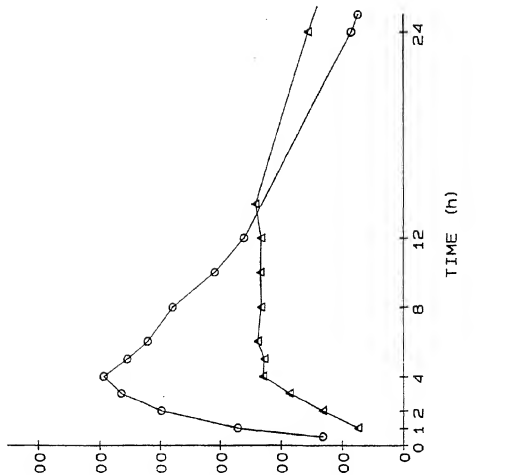


FIGURE 2 . MEAN (n=10) PLASMA CONCENTRATIONS OF METOPROLOL AFTER SINGLE-DOSE ADMINISTRATION. DOSE: METOPROLOL CORRESP. 200 MG TARTRATE SALT



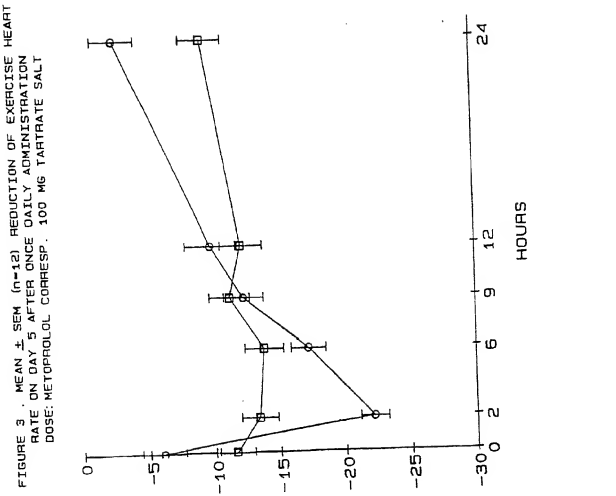


FIGURE 3 : MEAN ± SEM (n=12) REDUCTION OF EXERCISE HEART RATE ON DAY 5 AFTER ONCE DAILY ADMINISTRATION
DOSE: METOPROLOL CORRESP. 100 MG TARTRATE SALT
CONVENTIONAL TABLET
CR TABLET OF COATED BEADS
PERCENT
0
-5
-10
-15
-20
-25
-30
0
2
6
9
12
24
HOURS